(ii) * * *

(D) * * *

(*2*) Quantitative information comparing the level of cholesterol in the product per specified weight with that of the reference food that it replaces (e.g., ''Cholesterol lowered from 30 mg to 22 mg per 3 oz of product.'') is declared adjacent to the most prominent claim or to the nutrition label, except that if the nutrition label is on the information panel, the quantitative information may be located elsewhere on the information panel in accordance with § 101.2.

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Dated: March 24, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95–8067 Filed 3–31–95; 4:32 pm]

BILLING CODE 4160–01–P

21 CFR Part 876

[Docket No. 92N–0382]

Gastroenterology-Urology Devices; Effective Date of Requirement for Premarket Approval of Testicular Prosthesis

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to require the filing of a premarket approval application (PMA) or a notice of completion of a product development protocol (PDP) for the testicular prosthesis, a generic type of a surgically implanted medical device intended to simulate the presence of a testicle within the male scrotum. Commercial distribution of this device must cease, unless a manufacturer or importer has filed with FDA a PMA or a notice of completion of a PDP for its version of the testicular prosthesis within 90 days of the effective date of this regulation. This regulation reflects FDA's exercise of its discretion to require a PMA or notice of completion of a PDP for preamendments devices.

EFFECTIVE DATE: April 5, 1995.

FOR FURTHER INFORMATION CONTACT: Mark D. Kramer, Center for Devices and Radiological Health (HFZ–470), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–2194.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of January 6, 1989 (54 FR 550), the agency identified the testicular prosthesis as one of the high-priority devices that would be subject to PMA or PDP requirements. This rulemaking is consistent with FDA's stated priorities and Congress' requirement that class III devices are to be regulated by FDA's premarket approval review. This action is being taken under the Medical Device Amendments of 1976 (Pub. L. 94–295). The preamble to this rule responds to comments received on the proposal to require the filing of a PMA or a notice of completion of a PDP.

This regulation is final upon publication and requires a PMA or a notice of completion of a PDP for all testicular prostheses classified under § 876.3750 (21 CFR 876.3750) and all devices that are substantially equivalent to them. A PMA or a notice of completion of a PDP for these devices must be filed with FDA within 90 days of the effective date of this regulation. (See section 501(f)(1)(A) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 351(f)(1)(A)).)

In the **Federal Register** of November 23, 1983 (48 FR 53012 at 53024), FDA issued a final rule classifying the testicular prosthesis into class III (premarket approval). Section 876.3750 of FDA's regulations setting forth the classification of the testicular prosthesis intended for medical use applies to: (1) Any testicular prosthesis that was in commercial distribution before May 28, 1976, and (2) any device that FDA has found to be substantially equivalent to a testicular prosthesis in commercial distribution before May 28, 1976.

In the **Federal Register** of January 13, 1993 (58 FR 4116), FDA published a proposed rule to require the filing, under section 515(b) of the act (21 U.S.C. 360e(b)), of a PMA or notice of completion of a PDP for the classified testicular prosthesis and all substantially equivalent devices (hereinafter referred to as the January 1993 proposed rule). In accordance with section 515(b)(2)(A) of the act, FDA included in the preamble to the proposal the agency's proposed findings regarding: (1) The degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to meet the premarket approval requirements of the act, and (2) the benefits to the public from use of the device (58 FR 4116 at 4118).

The preamble to the January 1993 proposed rule also provided an opportunity for interested persons to submit comments on the proposed rule and the agency's proposed findings and, under section 515(b)(2)(B) of the act (21 U.S.C. 360e(b)(2)(B)), provided the opportunity for interested persons to request a change in the classification of the device based on new information relevant to its classification. Any petition requesting a change in the classification of the testicular prosthesis was required to be submitted by January 28, 1993. The comment period initially closed on March 15, 1993. Because of one request, FDA extended the comment period for 60 days to May 14, 1993, to ensure adequate time for preparation and submission of comments (58 FR 15119, March 19, 1993).

FDA did not receive any petitions requesting a change in the classification of the testicular prosthesis. The agency did receive a total of five comments in response to the January 1993 proposed rule. These represent comments from individuals, manufacturers, and professional societies. The comments primarily addressed issues relating to the significant risks associated with the use of testicular prostheses, and the preclinical and clinical data needed to support a future PMA application.

II. Summary and Analysis of Comments and FDA's Response

A. General Comments

1. One comment stated that it appears that FDA has chosen solid silicone elastomer testicular implants for disparate treatment from other silicone implants, even though the basic chemistry, ingredients, and many manufacturing steps are very similar to other class II implantable silicone products. The comment requested that FDA describe the differences between silicone gel-filled and solid silicone elastomer testicular implants, and between silicone gel-filled mammary prostheses and solid silicone elastomer testicular prostheses.

FDA disagrees with this comment. The testicular prosthesis was classified into class III in 1983 because insufficient information existed to determine that general controls would provide reasonable assurance of the safety and effectiveness of the device or to establish a performance standard to provide this assurance. The possible risks identified at the time of classification included: (1) The possible migration of silicone gel from the interior of the prosthesis to adjacent tissue (with or without rupture of the silicone elastomer shell), and (2) possible long-term toxic effects of the silicone polymers from which the prosthesis is fabricated. Therefore, requiring premarket approval for the testicular prosthesis is consistent with the intent to regulate this device as a class III device even in 1983. FDA notes that no requests for a change in

classification based on new information relevant to the classification of the device were submitted in response to the January 1993 proposed rule.

While FDA recognizes that some of the risks of silicone gel testicular prostheses may not necessarily apply to the solid silicone elastomer testicular prosthesis, the requirement that PMA's be submitted applies to the generic class of device comprised of all testicular prostheses. In addition, while FDA recognizes that some of the risks of silicone gel mammary prostheses may not necessarily apply to solid or silicone gel-filled testicular prostheses, the testicular prosthesis is similar in materials and construction to the silicone gel-filled breast prosthesis and, therefore, many of the risks associated with the use of the silicone gel-filled breast prosthesis may also be associated with the solid silicone and silicone gel-filled testicular prosthesis.

2. One comment stated that FDA's inclusion of prospective clinical data requirements in the proposed rule has resulted in a timetable for ultimate PMA submission that appears unreasonable and creates an undue burden on manufacturers. The comment stated that, had firms initiated PMA studies prior to the publication of the proposed rule, they could not have anticipated the new requirements.

FDA disagrees with this comment. More than 10 years have passed since these devices were classified into class III by final regulation. Furthermore, the risks to health detailed in the proposed rule remain consistent with those identified at the time of classification. FDA believes that, consistent with congressional intent, manufacturers have had notice and ample opportunity to gather the information necessary to provide reasonable assurance of the safety and effectiveness of these devices. It is not responsible to suggest that Congress intended manufacturers to remain passive and not develop PMA's until a regulation became final. Indeed, the act specifically requires submissions 30 months after the final classification of a preamendments device or within 90 days of a final regulation, whichever is later. (See section 501(f)(2)(B) of the act). Thus, it is clear that Congress intended that manufacturers anticipate a final regulation and be prepared to submit appropriate applications or discontinue distribution of their devices.

3. One comment stated that FDA's treatment of ear and testicular prostheses (both cosmetic implants) is disparate, because no psychological data was required for ear prostheses, and suggested that the proposed requirement for psychological data is unprecedented in the regulation process.

FDA disagrees with this comment. Ear and testicular prostheses are different devices, and have been classified by different panels. Ear prostheses, which are class II devices, were classified by the General and Plastic Surgery Panel. The review of such plastic surgery prostheses, such as chin prostheses, takes into consideration the quality of life of the patient. FDA notes that psychological data is only part of the effectiveness evaluation outlined in the proposed rule. Moreover, the request for such data is not unprecedented. Such data also were required in PMA's for silicone gel breast implants.

4. One comment stated that FDA should recognize that the solid silicone elastomer testicular prostheses available today are much improved in quality and are implanted using refined surgical techniques that minimize many risks implicated with their early use.

FDA acknowledges that the design of certain testicular prostheses and surgical techniques have evolved over time. FDA believes that neither the literature nor other data currently available to FDA definitively describe differences in the incidence of problems attributable to device design and/or variations in surgical procedures. Sufficient information exists identifying the risks detailed in the proposed rule as risks to health associated with the testicular prosthesis. FDA is requiring the submission of PMA's for this device in order to determine whether these risks can be controlled to provide reasonable assurance of the safety and effectiveness of these devices for their intended use. Even a decline in the incidence of these risks would not be a sufficient reason to abandon the regulation to require PMA's for testicular prostheses, absent a clear delineation and understanding of those risks.

5. One comment stated that Congress never intended ''old'' (preamendments) devices to be subjected to the same scrutiny as ''new'' devices under the premarket approval requirements.

FDA disagrees with this comment. FDA does not believe that Congress intended to differentiate between ''old'' and ''new'' devices with respect to the requirement that valid scientific evidence support a PMA approval. Neither sections 513(a)(3) nor 515(d) of the act (21 U.S.C. 360c(a)(3)) makes any distinction between ''old'' and ''new'' devices with regard to the requirements for approval. However, FDA does expect that more retrospective data, which, by its historical character, is generally less detailed and rigorous than prospectively gathered data, would be available for use in supporting the approval of ''old'' as opposed to ''new'' devices. Scientific evidence, including retrospectively gathered data, is acceptable to support a PMA approval, as long as the data constitute valid scientific evidence within the meaning of § 860.7(c)(2) (21 CFR 860.7(c)(2)).

6. One comment stated that the proposed rule did not address how amendments to PMA's submitted prior to panel review will be handled, and requested that the agency clarify the administrative procedures applicable to such PMA amendments.

PMA amendments submitted prior to advisory panel review will be evaluated to determine whether the information is sufficiently substantive to be considered a ''major'' amendment. A major amendment may extend the review period for up to 180 days as outlined in 21 CFR 814.37(c)(1).

7. One comment stated that FDA should refrain from promulgating the final rule without the specific guidance documents defining certain preclinical and clinical testing requirements.

FDA disagrees with this comment. Section 515(b) of the act does not require FDA to provide guidance for tests for PMA's prior to issuing a call for PMA's. While FDA outlined numerous manufacturing, preclinical, and clinical studies that suggest the content of a PMA for a testicular prosthesis, and issued a detailed guidance document for such PMA's in March 1993, that was discussed at a public meeting of the Gastroenterology and Urology Devices Advisory Panel in April 1993, these tests were suggestive and not intended to bind a PMA applicant to any specific study or set of studies. FDA's ''Draft Guidance for the Content of PMA Applications for Testicular Prostheses'' is available upon request from the Division of Small Manufacturers Assistance (HFZ–220), Center for Devices and Radiological Health, 1350 Piccard Dr., Rockville, MD 20850.

8. One comment suggested that FDA should reopen the dialogue with industry, scientific, and medical communities in order to develop a consensus on the exact scope and nature of some of the preclinical, material, and clinical data requirements.

FDA agrees that the dialogue with industry and the scientific and medical communities should remain open regarding the information needed to support a PMA. FDA staff have been and continue to be accessible to discuss these requirements as requested.

B. Risks

9. Two comments suggested that the list of risks do not represent ''significant risks'' of testicular prosthesis implantation. The contention was that FDA has not clearly differentiated between significant risks, potential risks, and potential adverse effects, and that FDA should limit identification of risks to those which have been reasonably shown to be significant risks. The comment noted that the potential effects may be divided into short-term effects and long-term effects.

FDA disagrees with this comment. The proposed rule clearly differentiated risks that have been observed with testicular prostheses from those that are potential risks. Erosion, extrusion, displacement, fibrous capsular contracture, infection, and silicone gel leakage are risks that have been reported specifically for the testicular prosthesis. Carcinogenicity, human reproductive and teratogenic effects, immune related connective tissue disorders (immunological sensitization), biological effects of silica, and degradation of polyurethane foam covering some implants were identified as potential risks that, based on review of all available information, FDA believes are relevant to the testicular prosthesis. While FDA agrees that the risks of any implant fall into the broad categories of short-term and long-term risks, FDA believes that many of the risks identified are both short and long-term in nature, rather than exclusively short or long-term.

10. One comment suggested that since erosion, extrusion, and/or displacement are readily correctable by medical intervention, and since revision surgery is possible if explant is necessary, they should not be considered significant risks. Furthermore, the comment suggested that displacement is not a commonly reported adverse event, nor can the prosthesis migrate to a variety of locations within the body.

FDA disagrees with this comment. Insufficient information is available to determine the frequency of these events or their effects. Furthermore, because these risks can necessitate revision surgery or explant, FDA believes they are appropriately identified as significant risks. However, FDA agrees that it was not accurate to state that the prosthesis can ''migrate to a variety of locations within the body,'' but notes that the prosthesis can migrate to, in front of, or behind the contralateral testis or above the scrotum. The discussion of this risk has been modified accordingly.

11. Several comments stated that certain references cited in the proposed rule failed to demonstrate a causal relationship or a strong association between the implantation of a testicular prosthesis and the onset of risks, such as carcinogenicity, teratogenicity, and autoimmune diseases or connective tissue disorders.

FDA agrees that the references cited do not establish or refute the existence of a causal relationship between testicular prostheses and these risks. However, the literature cited by FDA provides evidence that these potential risks are associated with the device and are not trivial. Consequently, investigation of these risks in support of a PMA is necessary.

12. Two comments regarding the potential carcinogenicity of silicone were received. The comments make the contention that the animal studies reported are irrelevant because the observed sarcomas were solely due to physical (solid state) carcinogenesis and such risks are not applicable to humans.

FDA disagrees with these comments. Carcinogenicity is a putative risk secondary to implantation of any material. After review of all available information, the agency continues to believe that carcinogenicity is a potential risk that must be assessed in a PMA.

13. Three comments were on the subject of reproductive and teratogenic effects of the testicular prosthesis. These comments stated that, because the majority of prostheses are placed in middle-aged to elderly men who have had testicular removal as treatment for prostatic cancer, the human reproductive concern is irrelevant. These comments also stated that: (1) There are no reports of adverse effects of testicular prostheses on reproduction, or teratogenic effects on offspring of patients with such prostheses; (2) FDA misinterpreted the results of the literature cited; and (3) only silicone rubber or silicone gel products which contain or are synthesized from phenylmethyl silicones have potential effects on the male reproductive system.

FDA agrees with the comments that, to date, there are no published studies showing reproductive toxic effects or teratogenic effects associated with implantation of silicone materials. While some authors may have concluded that silicone is not a teratogen, FDA believes that there have been no well-designed studies using silicone testicular implants to determine potential human reproductive and teratogenic risks. FDA believes that information in the form of well-designed, single generation animal studies would be appropriate. Additionally, a PMA applicant may choose to submit appropriate human studies, or properly gathered and analyzed historical data, to establish the teratogenic potential of a silicone testicular prosthesis.

FDA agrees that the requirement for reproductive toxicity and teratogenicity information for PMA's should apply for those silicone rubber or silicone gel testicular prostheses which contain or are synthesized from phenylmethyl silicones, but the agency notes that this testing should also be conducted for other silicones until the reproductive and teratogenic profiles of these materials are established.

Finally, FDA agrees that the human reproductive concern may not apply to some testicular implant recipients. However, because a sizable portion of the implant population consists of young males, the concern is relevant. After reviewing all available data, FDA believes that the prolonged contact young males would have with the device presents a potential risk of reproductive effects and teratogenicity in humans.

14. Two comments stated that fibrous capsule formation is a normal wound healing process and, in the case of a testicular prosthesis, aids in keeping the implant in place and preventing migration to other parts of the body. The comments stated that this response occurs following implantation of almost any material and should not be considered a complication or adverse event associated with implantation of testicular prostheses. One comment stated that the incidence rate of fibrous capsular contracture is low, while the second stated that it has never been reported; both argued that it should not be listed as a significant risk.

FDA agrees that fibrous capsule formation is a normal wound healing process that can occur following implantation of almost any material. The agency disagrees, however, that fibrous capsular contracture is not a significant risk of the testicular prosthesis. Fibrous capsular contracture may result in excessive scrotal firmness, discomfort, pain, disfigurement, and displacement of the implant. Moreover, sufficient information exists to identify capsular contracture as a risk to health associated with the testicular implant. FDA believes that literature case reports and product complaints to the manufacturer do not necessarily capture all problems with medical devices.

15. Two comments suggested that the incidence of infection occurs at a rate consistent with other prosthetic implant surgeries and is seldom serious and,

therefore, that infection should not be considered a significant risk.

FDA disagrees with this comment. While the incidence of infection may be similar to other prosthetic devices, data are needed to specifically quantify its incidence and effect. Infection often leads to surgical removal of the implant and, therefore, is a potentially serious adverse event. After review of all available information, FDA continues to believe that infection is a significant risk associated with the testicular prosthesis.

16. Several comments were received on the subject of immune related connective tissue disorders or immunological sensitization. The comments make the following contentions: (1) Silicone stimulates a cell-mediated response only when administered under extraordinary conditions with an adjuvant; (2) there is no evidence to date that hard silicone elastomer has immune system adjuvant properties; (3) recent surveys of populations of women with connective tissue disorders have demonstrated no increase in disease prevalence in women with silicone breast implants; and (4) since scientific studies of women with silicone mammary prostheses have not shown a risk for development of connective tissue disorders, implantees with silicone testicular implants, which have less than one thirtieth the volume of a breast implant, should also not be at risk of connective tissue disorders.

FDA disagrees with these comments. The adjuvant effect of silicone gel is established in animal studies (Ref. 1). A recent study (Ref. 2) suggests that some women with silicone gel-filled breast prostheses may develop atypical immunologic reactions. Therefore, the agency continues to believe that the potential risk of immune related connective tissue disorders or immunological sensitization to implanted silicone testicular prostheses must be assessed in a PMA.

17. One comment stated that, while the scientific evidence to date does not demonstrate any cause and effect relationship between the testicular silicone implant and the subsequent development of autoimmune diseases, additional research needs to be completed.

FDA agrees with this comment.

18. Two comments stated that fumed, amorphous silica is tightly incorporated into the silicone elastomer shell of the testicular prostheses and, as a result, has very different (and reduced) biological activity.

FDA does not believe that there is sufficient information available to conclude that amorphous (fumed) silica does not produce the same kind of biological effects as crystalline silica. Furthermore, while the silica reinforcer material may not be extractable, it can be potentially exposed or shed in the form of particles from the elastomer by the process of abrasive wear. Therefore, FDA believes it is necessary that data demonstrating the safety of amorphous silica should be submitted in PMA's.

C. Benefits

19. One comment stated that it is important to recognize the value of a psychological benefit to patients using these devices, and that although it is more difficult to document and quantify a psychological benefit than a physical benefit, the preponderance of evidence showing a psychological benefit should not be underestimated nor undervalued.

FDA agrees with this comment, and has outlined the data needed to demonstrate the psychological benefit of the testicular prosthesis.

D. Manufacturing

20. One comment stated that cooperation between manufacturers and raw materials suppliers is necessary in order to obtain the manufacturing data required in a PMA.

FDA agrees that a cooperative relationship between manufacturers and raw materials suppliers will make the manufacturing data requirements easier to complete, but the agency notes that much of the materials information needed is on the finished, sterilized device.

21. One comment suggested that the manufacturing information section should be revised to allow the referencing of master file submissions, with more limited chemical characterization (e.g., Fourier Transform Infrared Spectroscopy (FTIR)) to confirm chemical composition, and mechanical testing to establish criteria for lot to lot variability in the cured product.

FDA disagrees with this comment. While proprietary manufacturing information and, perhaps, testing results may be part of a master file, additional information beyond formulation data is needed to document the safety of the materials used to construct the device. The additional information must consist of testing that is more sensitive to process variation than routine FTIR and mechanical tests on the cured product. The chemical, physical, and mechanical properties of the final device are affected not only by the starting raw materials, but by the chemical reaction, processing, and subsequent sterilization of these raw materials to make the final device. Only the device manufacturer, not the raw material supplier, has control over these processes. Consequently, referral to a device master file is not, in itself, adequate to assess the safety of the final sterilized device.

22. One comment noted that the supply of silicone raw materials is in jeopardy due to market withdrawal by several manufacturers. This comment suggested that a guidance document is needed to determine acceptable equivalency and data requirements.

FDA agrees that market withdrawal of silicone raw materials by several manufacturers may limit their availability. In the **Federal Register** of July 6, 1993 (58 FR 36207), FDA published a notice of availability of a guidance entitled ''Guidance for Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials.'' The guidance describes the testing procedures to be followed by manufacturers in determining the equivalency of the materials.

E. Extraction Testing

23. One comment stated that the concept of exhaustive extraction and identification and quantification of all chemicals is relatively recent and thus requires method development and validation tantamount to the creation of a new science.

FDA disagrees with this comment. Numerous literature references describe extraction, identification, and quantification of individual silicone components from a variety of matrices using a variety of extraction solvents. While more limited, references exist for supercritical fluid extraction of the low molecular weight components from silicone elastomers. This is not a new science. FDA recognizes the difficulty in quantifying the amount of more than 35 separate components possible given the materials of interest, however present state-of-the-art allows this to be done.

24. One comment stated that FDA's request for molecular characterization of elastomer intermediates, outer shell, patch, and other component parts is not possible since, with the exception of the internal gel component, the parts are composed of solid cured elastomeric material. Furthermore, the comment stated that FDA's request for determination of residual volatile and nonvolatile cyclic compounds is a duplication of the requirement for analysis of extractables set forth in the preclinical data section of the proposed rule.

FDA agrees that this section was unclear. Because only a limited amount of chemical characterization can be

done on highly crosslinked polymers, it is important to characterize the immediate precursors to assure the quality of the base polymers and crosslinking agents. Regarding the determination of residual volatile and nonvolatile cyclic compounds, FDA agrees that this requirement should apply only to the individual structural components (outer shell, patch, internal gel, suture tab, polyurethane foam covering, and any other materials) as they are found in the final sterilized device as described in the preclinical data section, and should not apply to material intermediates and precursors.

25. One comment stated that the requirement of ''complete identification and quantification of all chemicals'' is untenable and unattainable, and should be modified to allow manufacturers to focus on identification and quantification of those substances whose presence in the finished device is known or reasonably anticipated based on composition of starting materials, known additives, reaction byproducts, and potential residues or contaminants from reagents used in processing.

FDA disagrees with this comment. Identification and quantification of the majority of chemicals below a molecular weight of 1,500 for silicones, as specified in the guidance, is possible. For other polymeric materials, different criteria may be acceptable and should be discussed with FDA on a case-by-case basis. While FDA agrees that knowledge of the formulation will assist in predicting what might be found in the final product, it will not delineate what or how much is actually in the final product nor assess how the manufacturing process will affect the final product. Knowledge of the formulation will also help in selecting the appropriate analytical methodology to be used for the analysis.

26. One comment stated that analysis of extractables and subsequent toxicity testing should be performed entirely on the final product, rather than separate structural components, and that FDA should establish threshold limits for extractives based on molecular characteristics.

FDA agrees with the first part of this comment, but notes that the analyst should be aware of the drawback to testing the final product in toto. For example, wide variation in the size of the structural components and their proximity to each other in the final device may result in erroneous conclusions being made regarding the chemical identity and source of extract components. Furthermore, the outside shell of an intact device may preclude exhaustive extraction of the interior gel within a reasonable period of time. Nor does testing of an intact device simulate a prosthesis that has ruptured in vivo. Separate testing of the individual components (materials/adhesives) of the final device is acceptable provided that the formulation of the test specimens is identical to the formulation of the materials used in the actual device and has been subjected to the same curing, post-curing, processing, and sterilization modes as the final whole device. Such testing would also allow an increase in specimen size to accommodate the collection of sufficient extract to perform any analytical and biocompatibility testing. Adjustment of the analytical results on a weight basis can then be calculated for the intact device. Regarding the establishment of threshold limits, FDA agrees in theory, but notes that present limited knowledge of toxicity based on molecular characteristics, especially with respect to siloxanes, makes the establishment of threshold limits impossible.

27. One comment stated that FDA should define what is meant by ''exhaustive extraction''.

FDA's ''Draft Guidance for the Content of PMA Applications for Testicular Prostheses'' provides detailed guidance on extraction for silicone implants. This guidance is available upon request from the Division of Small Manufacturers Assistance (HFZ–220) (see address above in section II A of this document).

F. Physical Testing

28. One comment stated that it seems unnecessary for FDA to require characterization of a physical or chemical property unless it is relevant to the intended use of the device.

FDA notes that no specific physical property tests were cited in the comment. FDA believes that all of the physical property tests identified in the proposed rule are relevant to the intended use of the device.

29. Two comments stated that the testicular prosthesis is too small to use the American Society for Testing and Materials (ASTM) test methods D412 and D624 as stated in the proposed rule, which specify specimen size and test methodology, based on a relationship between a ratio of thickness to area for a known coupon size and configuration. The comment suggested that the ASTM test methods can be used if slabs representing the device formulation are prepared for testing, according to both ASTM D412 and D624.

FDA agrees with this comment. The use of downsized dies for testing smaller samples obtained from finished sterilized devices may be employed. Test slabs mimicking the formulation of the materials used in the actual device and subjected to the same processing and sterilization modes could also be used. This would also apply to the samples used for testing of the integrity of adhered or fused joints. Evaluation of biodegradation effects on physical properties of elastomeric components could be accomplished by physical testing of test slabs explanted from animals.

30. One manufacturer noted that, in its experience, there has never been a case of a testicular implant failure from shell abrasion, and questioned the need for abrasion testing. The comment noted that only two explants had been received in the manufacturer's 9-year history with the device.

FDA disagrees with this comment. The fact that the manufacturer has received only two explanted devices in its 9-year history with the device is not a sufficient reason for dismissing abrasion as a potential failure mode for the device. In addition, other potential adverse effects are associated with abrasion, such as release of silica, inflammation, and granuloma formation.

G. Biocompatibility Testing

31. Two comments stated that mutagenicity and other toxicity testing be required to use mixtures of total extractables rather than individual components.

FDA agrees with this comment.

32. One comment noted that biodegradation testing may require miniature implants in animals, and suggested that the biodegradation studies should consist of microscopy studies, as well as chemical characterization which would be indicative of any degradation process.

FDA agrees with this comment.

33. One comment stated that histopathology should not be required for acute toxicity studies because the duration of the study is insufficient for developing tissue responses.

FDA agrees with this comment.

34. One comment stated that the preclinical requirements exceed the Tripartite Biocompatibility Guidance for Medical Devices (Ref. 3) and even the science of biocompatibility testing.

FDA disagrees with this comment. The agency notes that the biocompatibility requirements were based on the Tripartite Biocompatibility Guidance for Medical Devices.

35. One comment suggested that testing of nonpolar solvent extracts for a variety of biocompatibility tests is not

relevant to the devices currently on the market.

FDA disagrees with this comment. The proposed rule suggests that, at a minimum, ethanol, ethanol/saline (1:9), and dichloromethane should be used. Solvents should be chosen that are expected to solubilize the low molecular weight migrants in a reasonable period of time, thus facilitating exhaustive extraction—not to mimic in vivo conditions. Inasmuch as the chemical nature of all the migrants is not known, it is advisable to use solvents with varying chemical characteristics.

36. One comment suggested that for extracts composed of substances possessing innocuous structures and having low potential exposures, either no testing or only minimal testing should be required.

FDA disagrees with this comment. There is currently limited knowledge of what is and what is not ''innocuous'' based solely on chemical structure. The potential exposure can only be based on the maximum amount found in the final product by analytical tests. However, since polysiloxanes contain many, perhaps more than 35, chemical components as a byproduct of the synthesis, FDA agrees that it is difficult to individually test all components found in the extract. Therefore, FDA will accept testing of the mixtures of total extractables rather than of individual components.

37. One comment stated that the pharmacokinetics testing outlined requires methodology that does not currently exist for solid elastomeric silicone.

FDA agrees in general with the comment regarding solid elastomeric silicone products. However, if the solid elastomers contain leachable components, FDA believes they should be subjected to pharmacokinetics testing.

H. Clinical Investigations

38. Several comments suggested that many of the safety and effectiveness questions raised in the proposed rule can be addressed by evaluation of the available published clinical data, collection and analysis of retrospective epidemiological data and, if necessary, initiation of postmarketing followup studies.

FDA agrees that long-term retrospective epidemiological data, if collected properly, can be very useful in identifying long-term issues pertaining to safety and effectiveness. However, FDA believes it is necessary to require randomized (if at all possible), prospective studies to establish the short-term (in this case, up to 5 years or until physical maturity of the subject) safety and effectiveness data of the testicular implant. Only prospective data collected under a well-designed protocol can adequately address issues of safety and effectiveness relevant to the current population of implant users.

39. One comment stated that FDA focused almost exclusively on ''well-controlled studies'' while ignoring other valid scientific evidence as defined in § 860.7(c)(2).

FDA disagrees with this comment. Although § 860.7(f) does allow valid scientific evidence other than well-controlled investigations, § 860.7(e)(2) notes that ''The valid scientific evidence used to determine the effectiveness of a device shall consist *principally* [emphasis added] of well-controlled investigations.'' Therefore, well-controlled investigations are not only appropriate, but required, with other ''valid scientific evidence'' to be considered in a supporting role. In fact, FDA encourages the submission of all well-documented, valid retrospective data, which are presented in an organized manner.

40. One comment stated that FDA did not identify the duration of the clinical trial needed to establish safety and effectiveness, and suggested that while life-long data are ideally needed, some reduced amount of data should be identified to allow continued distribution of the testicular prosthesis.

FDA notes that the proposed rule suggested that 5-year clinical data, or data collected until the physical maturity of the subject (whichever occurs later) is needed, and that post-approval studies will be needed to address the various long-term issues identified.

41. Two comments requested clarification of what would constitute an adequate control, suggesting that the controls need to be tailored to the specific questions being asked, and that multiple control groups may therefore be necessary. One comment stated that meaningful control data may be either unimportant or impossible to obtain. One comment suggested that the patient should be his own control due to the difficulty in identifying and recruiting an appropriate control group for a male without one or both testicles.

FDA agrees that controls need to be tailored to the specific questions under investigation, and that multiple control groups may therefore be necessary. FDA strongly disagrees that ''meaningful control data may be unimportant.'' However, if ''meaningful control data may be * * * impossible to obtain'', the sponsor must rigorously demonstrate this for the relevant hypothesis. FDA agrees that it may be very difficult or impractical to recruit an appropriate control group. If the sponsor can satisfactorily demonstrate this to be the case, the subject may serve as his own control.

42. One comment noted that epidemiological clinical testing would require many years of patient enrollment to address only hypothetical concerns.

FDA agrees in part with this comment. FDA's ''Guidance to Manufacturers on the Development of Required Post-approval Epidemiologic Study Protocols for Testicular Implants'' permits manufacturers to document whether conditions are too rare to detect in a reasonable study. It also emphasizes that valid case-control studies and retrospective cohort studies are welcome. The guidance is available upon request from the Division of Small Manufacturers Assistance (HFZ–220) (see address above in section II A of this document).

43. One comment suggested that two generation human testing would be needed for teratology testing.

FDA believes that single generation animal studies, properly gathered and analyzed historical clinical data, or other valid scientific evidence would also be appropriate in determining the teratogenic potential of the testicular prosthesis.

I. Need for Psychological Data

44. One comment stated that the psychological benefits of the testicular prosthesis do not need to be evaluated using standardized testing and quantification of benefits because: (1) Studies are available in which patient satisfaction with testicular prostheses has been assessed; (2) the notion that the absence of one or both testicles produces adverse psychological effects on boys and adult males appears to be universally accepted; (3) several anecdotal reports strongly support the use of testicular prostheses for patients with congenital or other absence of testes; and (4) manufacturers make no claims regarding the psychological benefit of the device.

FDA disagrees with these comments. The studies cited were either so small as to be considered anecdotal, did not describe the assessment tools used, used no systematic assessment of the psychological impact of the prostheses, or consisted of particular subpopulations whose applicability to the general population would be questionable. These shortcomings underscore the need for FDA's request for a systematic assessment using reliable and valid measures of the

psychosocial consequences of testicular implants. Regardless of the actual claims made, it is clear that the testicular prosthesis is implanted for its psychosocial benefit to the implant recipient.

45. One comment stated that the intended use of the testicular prosthesis is to construct or reconstruct the size and contour of the male testicle, and that before and after size measurements would be sufficient to demonstrate effectiveness beyond any reasonable doubt. Furthermore, to expect manufacturers to conduct psychological testing in the absence of an FDA-recognized validated test instrument is not appropriate.

FDA disagrees with this comment. While before and after size measurements would be sufficient to show the anatomical effect of the implant, FDA believes that testicular prostheses are primarily used for the psychological benefit. FDA agrees with an earlier comment which stated that the psychological benefit should neither be underestimated nor undervalued. Finally, FDA notes that section 515(b) of the act does not require FDA to provide guidance for tests for PMA's prior to issuing a call for PMA's. While FDA outlined the principles of the psychological/psychosocial data needed in the proposed rule, in the ''Draft Guidance for Preparation of PMA Applications for Testicular Prostheses,'' and at a public meeting of the Gastroenterology and Urology Devices Advisory Panel in April 1993, these tests were suggestive and not intended to bind a PMA applicant to any specific study or set of studies.

46. One comment stated that requiring documentation of psychological benefits through further well-controlled presurgical, immediate postsurgical, and long-term psychological studies using standardized, validated test instruments is inappropriate and would appear to fall outside the intent of the act. Congress intended that medical devices perform as intended, not that they necessarily produce therapeutic effects.

FDA disagrees with this comment. Section 860.7(e)(1) states that there is ''reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device * * * will provide clinically significant results.'' FDA believes that it is necessary that a PMA demonstrate that the device has a beneficial therapeutic effect, rather than merely demonstrating that a device functions in accordance with its design.

47. One comment stated that psychological testing of the juvenile segment of the potential patient population is impractical and inappropriate, and that FDA should provide specific guidelines on any required psychological testing.

FDA agrees that it may not be feasible to effectively assess the psychosocial impact of testicular prosthesis implantation on children 12 years of age and younger. However, FDA believes that children over 12 years of age should be tested, since sexuality and the physical manifestations of sexuality are psychologically very important to pubescent and adolescent children. Manufacturers are encouraged to contact FDA regarding specific guidelines on this testing.

III. Findings With Respect to Risks and Benefits

A. Degree of Risk

1. *Extrusion/erosion of the testicular prosthesis*. Extrusion and erosion of the testicular implant through the scrotal wall are among the most common complications associated with the use of these devices. Prosthesis extrusion is usually associated with concurrent wound dehiscence in instances where the device was inserted through a scrotal incision. Skin erosion has been reported following implantation of the testicular prosthesis due to the presence of a Dacron suture tab, insertion of an oversized device, or aggressive dissection of the subdartos pocket, and could result in subsequent infection or device extrusion. It has been suggested that the rate of extrusion due to wound dehiscence is between 3 and 8 percent.

2. *Displacement of the testicular prosthesis*. Displacement, or migration, is another commonly reported adverse event. The prosthesis can migrate in front of or behind the contralateral testis or above the scrotum. Displacement can be caused by either inadequate scrotal distension prior to insertion or improper surgical placement/fixation.

3. *Fibrous capsular contracture*. Fibrous capsular contracture, the formation of a constricting fibrous layer around the prosthesis, has been associated with the presence of testicular implants. Capsular contracture may result in excessive scrotal firmness, discomfort, pain, disfigurement, and displacement of the implant.

Although the etiological factors of capsular contracture have not been reported with testicular implants, several factors have been suggested with the breast implant, including hematoma, infection, and foreign body reaction. Despite these reports, no single factor has been demonstrated to be the sole cause of contracture. The etiology of contracture is not understood.

4. *Infection*. Infection, a risk of any surgical implant procedure, is associated with the use of testicular implants. As in any implantation procedure, compromised device sterility and surgical techniques may be major contributing factors to this risk. Usually, the occurrence of infection necessitates the removal of the prosthesis. It has been suggested with the silicone gel-filled breast prosthesis that infection may also contribute to the early development of capsular contracture.

5. *Human carcinogenicity*. Carcinogenesis has been widely discussed as a reputed risk secondary to implantation of any material. Evidence from the literature indicates that, in animal studies, different forms of silicone have been associated with various types of cancer. Cases of several types of cancer in humans have been reported in association with various forms of implanted silicone.

6. *Human reproductive and teratogenic effects*. The effect of certain silicone compounds on the reproductive potential of the male is largely unknown. It has been reported that at least one form of organosiloxane, which is known to be present in some silicone gels, mimics estrogens in the male rat leading to rapid testicular atrophy.

Teratogenesis includes the origin or mode of production of a malformed fetus and the disturbed growth processes involved in the production of a malformed fetus. Studies using silicone fluid in animals have been minimal, and yield contradictory and inconclusive results. Prolonged contact with either the solid silicone device, or the silicone gel-filled membrane and its components, presents a potential risk of teratogenicity in humans. Additionally, the theoretical risk of abnormalities appearing later in life in normally appearing offspring also warrants investigation.

The risk of adverse reproductive and teratogenic effects from testicular implants exists only in the subset of patients who have a single prosthesis with a unilateral, functional testicle.

7. *Immune related connective tissue disorders—immunological sensitization*. Immunological sensitization may be a serious risk associated with the implantation of a testicular prosthesis. Immune related connective tissue disorders have been reported in women who have silicone gel-filled prostheses or who have had silicone injections in augmentation mammoplasty. There are clinical reports of several patients who

have undergone augmentation mammoplasty with silicone gel-filled breast prostheses and later presented with connective tissue disease-like syndromes. Because testicular prostheses consist of similar silicone elastomers and gels, further study of the potential risk of immune related connective tissue disorders in humans with these implants is warranted.

8. *Biological effects of silica.* Amorphous (fumed) silica is bound to the silicone in the elastomer of the testicular prosthesis, and may be fibrogenic and immunogenic. Fumed silica and the silicone shell each elicit cellular responses in rats. The biological effects of silica, particularly the immunologic component of these reactions, present a potential risk and need to be examined.

The following potential risk pertains only to the gel-filled silicone rubber testicular prosthesis:

9. *Silicone gel leakage and migration.* Silicone gel leakage and migration from the silicone elastomer envelope, either from rupture of the envelope or by leaking of the gel through the envelope (gel ''bleed''), are also significant risks of silicone gel-filled testicular prostheses. Rupture of the envelope with gel leakage and subsequent migration may be secondary to surgical technique or mechanical stresses such as routine manual massage, trauma, and wear on the envelope, and necessitates removal of the prosthesis. In addition to the above, silicone gel-filled breast implants, which are similar to testicular implants in materials and construction, are reported to ''bleed'' micro amounts of silicone through the intact silicone elastomer shell into the surrounding tissues. Although diffusion of silicone gel through the elastomer shell has not specifically been measured in the testicular prosthesis, gel bleed continues to be a theoretical risk with this device and needs to be evaluated. Migration of the gel into the human body presents the potential for development of adverse effects such as granulomas or lymphadenopathy. The ultimate fate of migrating silicone gel within the body is currently not well understood.

The following potential risk is associated only with those testicular prostheses that are polyurethane foam covered:

10. *Degradation of polyurethane foam.* The polyurethane foam material that has been used to cover some testicular prostheses is known to degrade over time with a potential breakdown product of 2,4 diaminotoluene (TDA), a known carcinogen in animals. The fate of the degraded product in vivo is unknown to date, and the use of this material in testicular implants may have been discontinued. Case reports of the polyurethane foam covered silicone gel-filled breast implant indicate that there is greater difficulty with the removal of this type of prosthesis due to a fragmented polyurethane shell and/or capsular tissue ingrowth. Foreign body responses have been reported concurrent with the use of the polyurethane foam covered testicular prosthesis in humans.

B. Benefits of the Device

The testicular prosthesis is intended to simulate the presence of a testicle within the male scrotum, and is indicated in subjects who are missing one or both testes due to either congenital or acquired reasons. Testicular prosthesis implantation is a discretionary surgical procedure performed for psychological, rather than for other medical reasons.

Testicular prostheses are commonly used to correct congenital anomalies in young males who are born without one or both testicles (i.e., testicular agenesis or atrophy). Additionally, such devices are often implanted subsequent to removal of one or both testes for one of several reasons: Malignant cancer of the prostate, testicular cancer, testicular torsion, cryptorchidism, failed orchiopexy, epididymitis/orchitis, or testicular trauma.

Men facing orchiectomy (removal of the testicles) may experience depression that accompanies this degenerative change in body image. Such feelings of depression have been equated to the experiences of women who have undergone mastectomy or hysterectomy. Shame and feelings of inferiority are common, and can lead to anxiety, personality changes, changes in one's customary lifestyle, fear of sexual rejection, and psychogenic impotence. It has also been reported that a visible defect in a child's genital region may result in feelings of inferiority, leading to social isolation. Such occurrences may produce psychologic problems, and have an affect upon the child's emotional development and sexual identity. Implantation of a testicular prosthesis may help to alleviate such feelings in males of all ages, thereby improving quality of life. The studies which have been published indicate that recipients of testicular prostheses exhibit a high degree of satisfaction with their surgery.

IV. Final Rule

Under section 515(b)(3) of the act, FDA is adopting the findings as published in the preamble to the proposed rule and is issuing this final rule to require premarket approval of the generic type of device, the testicular prosthesis, by revising § 876.3750(c).

Under the final rule, a PMA or a notice of completion of a PDP is required to be filed with FDA within 90 days of the effective date of this regulation for any testicular prosthesis that was in commercial distribution before May 28, 1976, or that has been found by FDA to be substantially equivalent to such a device on or before the 90th day past the effective date of this regulation. An approved PMA or declared completed PDP is required to be in effect for any such device on or before 180 days after FDA files the application. Any other testicular prosthesis that was not in commercial distribution before May 28, 1976, or that has not, on or before 90 days after the effective date of this regulation, been found by FDA to be substantially equivalent to a testicular prosthesis that was in commercial distribution before May 28, 1976, is required to have an approved PMA or declared completed PDP in effect before it may be marketed.

If a PMA or notice of completion of a PDP for a testicular prosthesis is not filed on or before the 90th day past the effective date of this regulation, that device will be deemed adulterated under section 501(f)(1)(A) of the act, and commercial distribution of the device will be required to cease immediately. The device may, however, be distributed for investigational use if the requirements of the investigational device exemption (IDE) regulations (21 CFR part 812) are met.

Under § 812.2(d) (21 CFR 812.2(d)) of the IDE regulations, FDA hereby stipulates that the exemptions from the IDE requirements in § 812.2(c)(1) and (c)(2) will no longer apply to clinical investigations of the testicular prosthesis. Further, FDA concludes that investigational testicular prostheses are significant risk devices as defined in § 812.3(m) and advises that, as of the effective date of § 876.3750(c), the requirements of the IDE regulations regarding significant risk devices will apply to any clinical investigation of a testicular prosthesis. For any testicular prosthesis that is not subject to a timely filed PMA or notice of completion of a PDP, an IDE must be in effect under § 812.20 on or before 90 days after the effective date of this regulation or distribution of the device for investigational purposes must cease. FDA advises all persons presently sponsoring a clinical investigation involving the testicular prosthesis to submit an IDE application to FDA no later than 60 days after the effective date

of this final rule to avoid the interruption of ongoing investigations.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) and (e)(4) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the manufacturers of these devices have been aware for a long time, more than 10 years, of the need to prepare PMA's for these devices, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

VII. References

The following references have been placed on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857 and may be seen by interested persons between 9 a.m and 4 p.m. Monday through Friday.

1. Naim, J., and R.J. Lanzafame, ''The Adjuvant Effect of Silicone Gel on Antibody Formation in Rats,'' *Immunological Investigations*, 22(2):151–161, 1993.

2. Bridges, A. J., C. Conley, G. Wang, D. E. Burns, and F. B. Vasey, ''A Clinical and Immunologic Evaluation of Women With Silicone Breast Implants and Symptoms of Rheumatic Disease,'' *Annals of Internal Medicine*, 118(12):929–936, 1993.

3. Tripartite Biocompatibility Guidance for Medical Devices, Office of Device Evaluation General Program Memorandum #87–1, April 24, 1987.

List of Subjects in 21 CFR Part 876

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 876 is amended as follows:

PART 876—GASTROENTEROLOGY–UROLOGY DEVICES

1. The authority citation for 21 CFR part 876 is revised to read as follows:

Authority: Secs. 501, 510, 513, 515, 520, 522, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 360, 360c, 360e, 360j, 3601, 371).

2. Section 876.3750 is amended by revising paragraph (c) to read as follows:

§ 876.3750 Testicular prosthesis.

* * * * *

(c) *Date premarket approval application (PMA) or notice of product development protocol (PDP) is required.* A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before July 5, 1995, for any testicular prosthesis that was in commercial distribution before May 28, 1976, or that has on or before July 5, 1995, been found to be substantially equivalent to a testicular prosthesis that was in commercial distribution before May 28, 1976. Any other testicular prosthesis shall have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.

Dated: March 13, 1995.

D. B. Burlington,

Director, Center for Devices and Radiological Health.

[FR Doc. 95–8383 Filed 4–4–95; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[TD 8591]

RIN 1545–AT28

Valuation of Plan Distributions

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Temporary regulations.

SUMMARY: This document contains temporary regulations that provide guidance to employers in determining the present value of an employee's benefit under a qualified defined benefit pension plan, for purposes of the applicable consent rules and for purposes of determining the amount of a distribution made in any form other than in certain nondecreasing annuity forms. These temporary regulations are issued to reflect changes to the applicable law made by the Retirement Protection Act of 1994 (RPA '94), which is part of the Uruguay Round Agreements Act of 1994. RPA '94 amended the law to change the interest rate, and to specify the mortality table, for the purposes described above. The text of these temporary regulations also serves as the text of the proposed regulations set forth in the notice of proposed rulemaking on this subject in the Proposed Rules section of this issue of the **Federal Register**.

DATES: These regulations are effective April 5, 1995.

These regulations apply to plan years beginning after December 31, 1994, except as provided in § 1.417(e)–1T(d)(8) and (9).

FOR FURTHER INFORMATION CONTACT: Linda S. F. Marshall, (202) 622–4606 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Short Description

The temporary regulations in this document set out rules for computing the amount of any benefit under a qualified defined benefit pension plan that is paid in any form other than certain annuity forms. These temporary regulations reflect changes made to the law in the Retirement Protection Act of 1994 (RPA '94) Pub. L. 103–465. Under the new law, if the annuity benefit an employee could receive under the plan is converted to a different form of benefit, the non-annuity benefit cannot be less than the value that would be determined using legally required assumptions regarding life expectancy (mortality table) and interest rate. This ensures that the non-annuity benefit will not be less valuable than the annuity benefit.

Under these temporary regulations, the mortality table used under the new law is the mortality table published by the IRS (currently a mortality table commonly used by state insurance commissioners). The interest rate used under the new law is the interest rate on 30-year Treasury securities, as published by the IRS. These temporary regulations allow an employer to choose a monthly, quarterly, or annual period during which the plan's interest rate remains constant, and allow an